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1. Your reference — 86.61.70445/001

2. Patent application number *(The Patent Office will fill in this part)* — **9915718.2** — 05 JUL 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Nycomed Amersham plc
Amersham Laboratories
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Patents ADP number *(if you know it)* 7395220051

If the applicant is a corporate body, give country/state of incorporation — United Kingdom

4. Title of the invention — Products and Methods

5. Name of your agent *(if you have one)* — Frank B. Dehn & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

179 Queen Victoria Street
London
EC4V 4EL

Patents ADP number *(if you know it)* — 166001

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

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Yes

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11. **I/We request the grant of a patent on the basis of this application.**

Signature [signature] **Date** 5 July 1999

12. **Name and daytime telephone number of person to contact in the United Kingdom**

Dr. Annabel Beacham
01273 244200

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70445B.201

Products and Methods

This invention relates to radiotherapy. More particularly it relates to radioactive sources for use in brachytherapy and to methods for the manufacture of such sources.

Brachytherapy is a general term covering medical treatment which involves placement of a radioactive source near a diseased tissue and may involve the temporary or permanent implantation or insertion of a radioactive source into the body of a patient. The radioactive source is thereby located in proximity to the area of the body which is being treated. This has the advantage that a high dose of radiation may be delivered to the treatment site with relatively low dosages of radiation to surrounding or intervening healthy tissue.

Brachytherapy has been proposed for use in the treatment of a variety of conditions, including arthritis and cancer, for example breast, brain, liver and ovarian cancer and especially prostate cancer in men (see for example J.C. Blasko et al., *The Urological Clinics of North America*, **23**, 633-650 (1996), and H. Ragde et al., *Cancer*, **80**, 442-453 (1997)). Prostate cancer is the most common form of malignancy in men in the USA, with more than 44,000 deaths in 1995 alone. Treatment may involve the temporary implantation of a radioactive source for a calculated period, followed by its removal. Alternatively, the radioactive source may be permanently implanted in the patient and left to decay to an inert state over a predictable time. The use of temporary or permanent implantation depends on the isotope selected and the duration and intensity of treatment required.

Permanent implants for prostate treatment comprise radioisotopes with relatively short half lives and lower energies relative to temporary sources. Examples of permanently implantable sources include iodine-125 or palladium-103 as the radioisotope. The radioisotope is generally encapsulated in a titanium casing to form a "seed" which is then implanted. Temporary implants for the treatment of prostate cancer may involve iridium-192 as the radioisotope.

Recently, brachytherapy has also been proposed for the treatment of restenosis (for reviews see R. Waksman, *Vascular Radiotherapy Monitor*, 1998, 1, 10-18, and *MedPro Month*, January 1998, pages 26-32). Restenosis is a renarrowing of the blood vessels after initial treatment of coronary artery disease.

Coronary artery disease is a condition resulting from the narrowing or blockage of the coronary arteries, known as stenosis, which can be due to many factors including the formation of atherosclerotic plaques within the arteries. Such blockages or narrowing may be treated by mechanical removal of the plaque or by insertion of stents to hold the artery open. One of the most common forms of treatment is percutaneous transluminal coronary angioplasty (PTCA) - also known as balloon angioplasty. At present, over half a million PTCA procedures are performed annually in the USA alone. In PTCA, a catheter having an inflatable balloon at its distal end is inserted into the coronary artery and positioned at the site of the blockage or narrowing. The balloon is then inflated which leads to flattening of the plaque against the artery wall and stretching of the artery wall, resulting in enlargement of the intraluminal passage way and hence increased blood flow.

PTCA has a high initial success rate but 30-50% of patients present themselves with stenotic recurrence of the disease, i.e. restenosis, within 6 months. One treatment for restenosis which has been proposed is the use of intraluminal radiation therapy. Various isotopes including iridium-192, strontium-90, yttrium-90, phosphorus-32, rhenium-186 and rhenium-188 have been proposed for use in treating restenosis.

Conventional radioactive sources for use in brachytherapy include so-called seeds, which are sealed containers, for example of titanium or stainless steel, containing a radioisotope within a sealed chamber but permitting radiation to exit through the container/chamber walls (US-A-4323055 and US-A-3351049). Such seeds are only suitable for use with radioisotopes which emit radiation which can penetrate the chamber/container walls. Therefore, such seeds are generally used with radioisotopes which emit γ-radiation or low-energy X-rays, rather than with β-emitting radioisotopes.

Brachytherapy seeds comprising a coating of radioactive silver iodide on a silver wire encapsulated inside a titanium container are known in the art (US-A-4323055). Such seeds provide radiation emission which is equivalent to between 0.1 and 100 millicuries of radioactivity. Such seeds are available commercially from Medi-Physics, Inc., under the Trade Name I-125 Seed® Model No. 6711.

Other conventional brachytherapy seeds comprise titanium containers encapsulating ion exchange resin beads onto which a radioactive ion, for example I-125, has been adsorbed (US-A-3351049). The immobilisation of a radioactive powder within a polymeric matrix has also been proposed (WO97/19706).

US-A-4323055 discloses activities of up to 100 mCi/seed, and seeds based on metal wires have not demonstrated the ability to carry very high levels of radioactivity. With radioactive seeds based on metal wires there is also the disadvantage that some of the radioactivity is absorbed by the wire itself. The amount of radioactivity absorbed by the wire increases as the atomic number of the metal used to form the wire increases. The precise amount of attenuation will be a function of the dimensions of the wire. For example, with a silver iodide-125 coated 0.5 mm diameter silver wire, up to about 20% of the radioactivity is absorbed by the wire itself. To manufacture a radioactive seed of a certain activity, extra radioactivity must be loaded onto the wire to take into account the absorption of some of the activity by the wire and also by the seed container. As the desired activity of the seed increases, so does the cost of the extra percentage amount of radioactivity which must be loaded onto the wire.

Attempts to manufacture high activity radioactive seeds comprising radioactive anions adsorbed onto ion exchange resin beads as in US-A-3351049 have not been completely successful, due we believe to the adverse effect of the radiation on the polymer bonds of the beads themselves. We have found there to be a tendency for the beads to degrade under the influence of high levels of radioactivity, leading to unreliable results.

There is still a need for a high activity radioactive source which is suitable for use in brachytherapy, and for methods to manufacture such sources. Such sources may be useful for the temporary brachytherapy of cancers and proliferative diseases, and especially for the prevention of restenosis following PTCA.

As one aspect of the invention there is therefore provided a radioactive source for use in brachytherapy, preferably a sealed source, comprising a radioactive isotope of iodine adsorbed on the surface of a suitable substrate, with the proviso that the substrate is not an ion exchange resin. Preferably, the source has an activity in the range of about 200 mCi to about 1200 mCi, preferably 300 mCi to 1000 mCi, and more preferably 400 mCi to 600 mCi.

Suitable radioisotopes of iodine are iodine-125, iodine-131 and iodine-123. Preferred due to its longer half life is iodine-125. As used herein, wherever the term iodine-125 is used, this should be interpreted as extending to iodine-131 or iodine-123.

The radioisotope of iodine may be present in the form of iodide ions or in the form of an iodine-containing compound. As used herein, the term "iodine-containing compound" includes molecular iodine or any compound containing covalently bonded iodine. Examples of suitable compounds include an iodohalogen compound such ICl, an organic compound containing a carbon-iodine bond, an iodoso-compound such as iodosobenzene, phenyliodoso diacetate, and o-iodosobenzoic acid, a diaryliodinium salt such as diphenyliodinium bromide and diphenyliodinium iodide wherein either or both of the iodine atoms may be a radioisotope of iodine, an N-iodoamide such as N-iodosuccinimide, an iodoxyaryl compound such as iodoxybenzene, or a covalently bound inorganic iodine compound such as tributyltin iodide.

Preferably, the sources of the invention comprise a sealed container, for example a substantially cylindrical tubular container made of metal or some other suitable

material, having a cavity in which a suitable amount of iodine-125 is present.

The container material should be corrosion resistant, compatible with body fluids and non-toxic and should not unduly absorb the X-ray radiation emitted from the radioisotope. Suitable containers include those made of low atomic numbered metals such as titanium or stainless steel. Higher atomic number metals such as gold, copper or platinum result in too much radiation attenuation to be useful *per se*. However, they may be useful for plating over certain low atomic number metals such as beryllium which would otherwise be too toxic if used without an outer coating. Titanium, titanium alloys or stainless steel are preferred metals for the container. Other suitable container materials include inert synthetic materials, for example Teflon™. The container is preferably completely sealed inside so there is no danger of leakage.

The source should be of an overall size and dimensions suitable for its intended use. For example, the overall dimensions of each radioactive source should preferably be such that it can be delivered to the treatment site using conventional techniques, for example it can be loaded inside a conventional catheter for delivery to the site of restenosis. Seeds for use in the treatment of prostate cancer, for example, are typically substantially cylindrical in shape and approximately 4.5 mm long with a diameter of approximately 0.8 mm, such that they may be delivered to the treatment site using a hypodermic needle. For use in the treatment of restenosis, a source should be of suitable dimensions to be inserted inside a coronary artery, for example with a length of about 10 mm and a diameter of about 1 mm, preferably a length of about 5 mm and a diameter of about

0.8 mm, and most preferably with a length of about 3 mm and a diameter of about 0.6 mm. Sources for use in the treatment of restenosis are typically delivered to the treatment site using conventional catheter methodology.

The substrate may be any material which is able to adsorb iodide ions or an iodine-containing compound and which is sufficiently stable to radiation to allow processing of the substrate into a brachytherapy source once the iodine radioisotope has been adsorbed. Preferably, the substrate is in the form of a substantially rigid body, for example a rod, filament or sphere. Preferably, the substrate is porous so that it has a large surface area available for adsorption. The substrate may also be in powdered form.

Suitable substrates include carbon, alumina, zeolites, titanium oxides, silica and silicon oxides, zeolite-type trivalent metal silicates, metal phosphates and hydroxyphosphates including hydroxyapatite, calcium hydroxyapatite, glassy materials, aluminium nitride, ceramics, radiation resistant polymers and natural materials such as bone, coral, coal, limestone, cellulose, starch, agar, gelatin, chitin, and hair either alone or woven together to make more substantial rods, and molecular sieve materials. A preferred substrate is carbon, and in particular activated carbon. Suitable activated carbon is available in the form of activated charcoal from American Norit Co., Inc. under the trade names Darco® and Norit®. Preferably the substrate comprises elements of low atomic number such that the absorption of radioactivity by the substrate is minimized. Preferably, the substrate is also of low density to help minimize absorption of radiation. For these reasons, carbon is particularly preferred.

For the adsorption of iodide ions, positively charged substrates are preferred. For example, ceramics at a pH below their isoelectric point (i.e. their pI) will express a positive surface charge which will attract negatively charged iodide anions.

Suitable substrates for the adsorption of molecular iodine include materials comprising amide bonds, for example peptides and proteins, polyvinylpyrrolidone (PVP), and graft copolymers, block polymers, and blends of polymers which contain amide bonds.

If the substrate is carbon, it may be in the form of a filament, rod, sphere, powder, particles, dust, compressed powder, carbonized polymers including starch, cellulose, chitin, agar or gelatin, carbon yarn available form Alpha Aesar, and carbonized polymers derived from acetylene, charcoal, soot or graphite including graphite fibres and rods, or a clathrate, fullerene or other carbon cage.

The iodine-125 may be in the form of molecular iodine (i.e. $^{125}I_2$). Alternatively, an organic compound which adsorbs onto the chosen substrate may be iodinated with ^{125}I and the iodinated compound then adsorbed onto the substrate. Organic compounds which adsorb onto a desired substrate may be known in the art or may be identified using routine experimentation.

Any known method for the iodination of organic compounds may potentially be adapted to use a radioactive isotope of iodine in place of a "cold" isotope. For example, iodide can be reacted with an organic molecule to form a bond between the iodide atom and a carbon atom on that molecule. For example, radioactive sodium iodide can be reacted with tyrosine to afford radiolabelled tyrosine.

In addition, methods for the covalent attachment of radioisotopes of iodine to organic molecules are known in the art, for example in Parker, C.W. "Radiolabelling of Proteins" in Methods in Enzymology, Vol. 182, 721 (1990); Noel, J-P. "La synthese radioactive avec le carbone 14, le tritium, le soufre 35 et l'iodi 125, L'Act. Chim. (R), 1997, 7, 5-13. (Radioactive synthesis with carbon 14, tritium, sulfur 35 and iodine 125. Actual. Chim (1997), (7), 5-13); Scherberg N.H. and Refetoff S. "Radioiodine Labelling of Ribopolymers for Special Applications in Biology", Methods in Cell Biology (1975) 10, pages 343-359 (Chaptern 19); and Baldwin, R.M., "Chemistry of Radioiodine", Appl. Radiat. Isot. Vol. 37, No.8, pp 817-821, 1986, all of which are incorporated by reference. Reagents and methods useful for radioiodination of organic molecules can also be found in the Pierce Catalog and Handbook, e.g., 1994-1995 edition, page T-335, Technical Section, "Iodination" (incorporated by reference). Preferred organic compounds for iodination include tyrosine phenylalanine either alone or as a dimer or polymer, tyrosine, phenylalanine containing peptides and proteins, phenols, and aromatic molecules with a reactive site for iodination; hydroxyaromatic compounds capable of enol-keto type tautomerism such as a phenolic compound containing a hydrogen in the ortho- or para-position, for example catechol or poly(3,4-dihydroxystyrene) which can be prepared by latex polymerization or by limited coalescence free radical polymerization of 1-vinyl-3,4-methoxystyrene followed by treatment with boron tribromide at low temperatures in methylene chloride; and aryldiazonium compounds which are known to form aryl iodides in a Sandmeyer-type reaction in the presence of potassium iodide (see Lucas H.J. and Kennedy E.R., Org. Syn., Coll. Vol. 2, 351, 1943 (incorporated by reference)), for example the diazonium salt of anthranilic acid can provide diiodobenzene according to the method of

Friedman L. and Logullo F.M., Angew. Chem., 77, 217, 1965 (incorporated by reference).

The substrate is preferably of a suitable size and dimensions to fit inside a container to form a sealed source. For example, the substrate may be rod-like or substantially spherical. However, the substrate may be any size or shape suitable for irradiating the lumen of occluded blood vessels for the prevention of restenosis, and the size and shape of the container may be chosen depending on the dimensions of the substrate. A source may comprise one or more substrates, or a plurality of substrates combined together, for example by compression and/or use of a suitable binder.

A plurality of substrates may be combined, optionally with the use of a binder. A binder is a material that can bind two or more activated substrates or a plurality of substrates together to form a larger composite.

A binder may be cohesive agent such as a glue, for example crazy glue and its approved medical grade counterpart Dermabond™, available from Ethicon, and other polymerised cyanoacrylate esters, an adhesive such as a hot melt adhesive, or a polymer such as polvinyl alcohol, polyvinyl acetate, poly(ethylene-co-vinyl acetate) and partially hydrolyzed poly(ethylene-co-vinyl acetate) polymers, polyvinylpyrrolidone or polyvinyl chloride. Also useful as binders are carbohydrates such as sucrose, mannitol, lactose, and the like, dextran, and cyclodextran; amino acids and proteins such as albumin; and salts such as alkali metal and alkaline earth metal salts of halides, sulfates, phosphates, and nitrates. Binders comprising lower atomic weight elements are preferred in order to minimize the absorption of radioactivity by the binder.

Preferably, the substrate body is in the form of a rod. A single container may contain only one substrate which occupies substantially all of the cavity inside the container. Alternatively, each container may contain two or more substrates, for example optionally separated by a suitable spacer. Preferably, the substrate arrangement will be such that there is a uniform radiation field around the source.

The level of radioactivity of a substrate prepared using the method of the invention will depend in part on the amount of radioactive iodine used in the method. The amount of iodine-125 required to provide a source of given activity will depend in part on the amount of radiation absorbed by the substrate and by the container. The amount of attenuation in any given case can be readily determined by a skilled person, for example by trial and error experimentation or by calculation.

The sources of the invention may be prepared by exposing a suitable substrate to a source of iodide ions or an iodine containing compound, for example to a source of molecular $^{125}I_2$ or an ^{125}I-containing organic compound. For reasons of safety, it is preferred not to use molecular $^{125}I_2$ due to its volatility.

As a further feature of the invention there is therefore provided a method for preparing a substrate suitable for use in a brachytherapy source, the method comprising exposing a substrate to a source of iodide-125 ions or an iodine-125 containing compound such that the iodide ions or the iodine-125 containing compound is adsorbed onto the surface of the substrate. Preferably, the iodine-125 containing compound is molecular $^{125}I_2$ or an ^{125}I-containing organic compound.

The iodide ions may be present as a solution of a soluble iodide salt in a suitable solvent, for example a solution of potassium or sodium iodide-125 in water.

Pegylated substrates, such as Eichrom's ABEC® (Aqueous Biphasic Extraction Chromatography) resins, may be used to selectively adsorb iodine (in the form of iodide, iodine or triiodide) from concentrated solutions of certain salts. Once loaded with iodine and dried, the substrates may be encapsulated in a container to form a brachytherapy source.

The iodine-125 containing compound may be present in solution in a suitable solvent. Alternatively, if the compound is a liquid it may be used neat. The substrate may alternatively be exposed to a vapour of $^{125}I_2$ or an ^{125}I-containing organic compound.

The substrate should be exposed to the iodide ions or to the iodine-containing compound for a sufficient period of time for the desired level of radioactivity to adsorb onto each substrate. Suitable exposure times may be determined by routine experimentation, for example by monitoring the level of non-adsorbed radioactive iodine remaining in the reaction medium.

If the iodine is in the form of an iodine-containing organic compound, the adsorption may take place in the same reaction vessel as the iodination reaction. For example, the substrate may be added to the reaction mixture after the iodination reaction has occurred such that the iodinated product is adsorbed onto the substrate without the need for any isolation of the iodinated product. The substrates onto which the iodine-125 has been adsorbed may then be isolated from the reaction

mixture, for example by filtration, dried if necessary and loaded into suitable containers to form radioactive sources for use in brachytherapy.

After the adsorption, the substrate may be further processed if required. For example, a plurality of substrates may be formed into a composite by the application of pressure and/or by the use of a binder. In one aspect of the invention, low melting binders may be melted and mixed with an activated carbon substrate containing adsorbed iodine-containing molecules, and then molded, cast or formed into a desired shape such as a thin rod, pellet, strip, wire, annulus or tube, and then cooled. The temperature should be below the temperature needed to de-adsorb the iodine-125 containing compound from the activated carbon. In another aspect of the invention, the binder may be mixed with an activated carbon substrate containing adsorbed iodine-containing molecules, and then moulded, cast or formed into a desired shape under pressure.

If the substrate comprises silver ions or ions of some other metal which forms an insoluble iodide salt, the substrate may be exposed to a solution of iodide-125, for example a solution of $Na^{125}I$, such that an insoluble iodide salt will form on the substrate. Such a method comprises a further feature of the invention. Substrates comprising silver ions include silver ion-containing zeolites or substrates such as polyvinyl alcohol, agar, gelatin, silica, carbonaceous materials or carbon yarn which have been previously exposed to a source of silver ions, for example to a solution of a silver salt.

Preferably, a sufficient amount of radioactive iodine is used in the method of the invention to produce substrates with activity levels in the range of about 240

mCi to about 1 Curie. Such substrates may, for example, be incorporated into radioactive sources for use in brachytherapy which have an activity of about 200 mCi to about 900 mCi.

In order for substantially all of the radioactive iodine to adsorb onto the surface of the substrate, the substrate and the reaction medium are preferably agitated. Preferably, the agitation takes the form of rotation of the reaction vessel such that the substrates "tumble" or roll in the reaction medium with each rotation.

For example, if the reaction vessel comprises a sealed individual vial, the vial may be rotated vertically end over end such that the contents tumble from end to end of the vial with each rotation. Rotation at a speed of 20 to 60 rpm is suitable.

Alternatively, the reaction vessel may be rotated at an angle to the horizontal such that the substrate rolls over in the reaction medium on each rotation. An angle of approximately 30° is suitable.

Suitable agitation of the reaction mixture also helps to ensure that maximum iodine uptake occurs, and that the uptake is uniform over the entire surface of the substrate.

The radioactive sources of the invention may be used as temporary implants for the treatment of cancers, for example head and neck cancers, melanoma, brain cancers, non-small cell lung cancer, breast cancer and ovarian, uterine and cervical cancer and other diseases including proliferative diseases, arthritis, urethral stricture and fibroid uterine tumours. Due to their high levels of radioactivity, it is unlikely that the sources will be

useful for permanent implantation brachytherapy. The sources may also be useful in the prevention of restenosis following PTCA.

As a further aspect of the invention there is provided a method of treatment of a condition which is responsive to radiation therapy, for example cancer and especially restenosis, which comprises the temporary placement of a radioactive source comprising an amount of iodine-125 adsorbed on the surface of a suitable substrate, with the proviso that the substrate is not an ion exchange resin, at the site to be treated within a patient for a sufficient period of time to deliver a therapeutically effective dose.

Preferably, the method of treatment of the invention is employed to inhibit restenosis at a site within the vascular system of a patient which has previously been subjected to PTCA.

The invention will be further illustrated by the following non-limiting Examples.

Example 1

Precipitation of Silver Iodide onto polyvinyl alcohol (Ivalon) Particles

In a small beaker, 1 g of PVA particles (150-250 microns) was equilibrated with a 0.5 molar solution of silver nitrate for 1 hour. At the end of the hour, the particles were allowed to settle to the bottom of the beaker and the supernatant was decanted to be replaced with 50 ml of distilled water. The particles were rinsed 3 times this way to prepare them for the final step. After decanting as much water as possible after the 3rd rinse, the particles were equilibrated with a solution of potassium iodide for 1 hour. Afterwards, the particles were again rinsed with water and then suspended in a small volume of saline for further testing.

A 1 ml HPLC sample tube was used to transport the sample to the Center for Imaging and Pharmaceutical Research (CIPR) at the Massachusetts General Hospital for imaging in a Toshiba CT scanner at 80 kV. This initial sample of PVA with AgI precipitated onto it was measured as 441 Hounsfield Units (HU) in saline. The conventional wisdom is that every 35 HU = 1 mg silver iodide or approximately 0.5 mg of iodide, and thus it can be estimated that 6.6 mg of iodide/ml of close packed particles is present in this sample or approximately 50 µg of iodide per particle. At a specific activity of 12 Curies/mg, each particle would have approximately 600 mCurie of radiation on board.

Example 2

Multiple Precipitations onto Polyvinyl alcohol (Ivalon) Particles

A suspension of polyvinyl alcohol (PVA) particles was prepared as in Example 1 above. At the end of the water rinse after the addition of potassium iodide, the particles were again exposed to a solution of silver nitrate for another hour. The suspension was then rinsed with water before a second aliquot of potassium iodide was added to precipitate a second layer of silver iodide. This was then repeated for a portion of the sample for a third precipitation of silver iodide onto the PVA particles. The particles were imaged at Massachusetts General Hospital with the following results:

Preparation	Contrast of Saline (Hounsfield Units)	Estimated µg I/particle	Activity* mCi/part
AgI (1)	441	50	600
AgI (2)	1758	200	2400
AgI (3)	2434	275	3300

* assuming 12 Curies/mg specific activity of ^{125}I.

Thus, it is clear that multiple layers of silver iodide can be deposited onto the PVA particles to obtain a wide range of iodide loadings and activities.

Example 3

Precipitation of AgI onto a zeolite

Zeolites containing silver ions were purchased from Aldrich as 1.6 mm pellets and 20 mesh spheres with a

composition of $Ag_{7.6}Na_{0.4}[(AlO_2)_8(SiO_2)_{40}]$ and $Ag_{84}Na_2[(AlO_2)_{86}(SiO_2)_{106}]$, respectively. Upon exposure of these ceramic materials to a solution of sodium iodide, they changed in appearance from a silver colour to a yellow-green demonstrating the formation of AgI within the zeolite itself. The amount of iodide taken up was not confirmed, but theoretically the materials possess 220 mg of Ag/gram in the zeolite pellets and 350 mg of Ag/gram in the zeolite spheres which could bind to an equivalent amount of iodide in the formation of silver iodide.

Example 4

Precipitation of AgI in a natural carbon source

Agar or gelatin at an appropriate concentration is prepared with water and a silver salt (silver nitrate), filled in glass or fused silica tubes and allowed to become a solid at room temperature. The glass tubes are cut to the desired length and soaked in a solution of sodium iodide to create silver iodide trapped in the agar or gelatin phase of the tubing.

Example 5

Precipitation of AgI on solidified carbonaceous materials and silica substrates

Natural carbonaceous sources such as wooden toothpicks and rice grains, and glass tubing were first coated with a silver coating by adding the articles to solution A: a 7% solution of sodium carbonate, and mixed well for a few minutes. Then an equivalent amount of the following solution mixture was added and allowed to mix at room temperature for five minutes: solution B: 0.72% silver nitrate, 0.72% ammonium nitrate, and 1.31% formaldehyde.

The articles were removed and air dried. The articles had a dull to shiny silver coating. After drying, the articles were immersed in a NaI solution with potassium ferricyanide and mixed well. After ten minutes, the articles were removed. The silver coating now had a yellow-green colour denoting formation of silver iodide.

Example 6

Solution A is prepared as a 7% solution of sodium carbonate in water.
Solution B is prepared as 0.72% silver nitrate, 0.72% ammonium nitrate, and 1.31% formaldehyde in water.
Solution C is prepared as 1.0% NaI solution and 2.0% potassium ferricyanide solution in water and contains 600 mCi of ^{125}I.

A 5 mm piece of carbon yarn 0.076 mm diameter obtained from Alpha Aesar in 5 metre lengths is placed in an aliquot of solution A. To this is added an aliquot of solution B at room temperature. After about 5 minutes, the silver-coated carbon yarn is isolated by filtration, air-dried, and immersed in an aliquot of solution C for not less than 30 minutes. The excess solution is removed by aspiration, and the now-radioiodine-containing yarn is dried in a stream of nitrogen.

Example 7

The method of Example 1 is repeated using $^{125}I^-$.

Example 8

The method of Example 2 is repeated using $^{125}I^-$.

Example 9

The method of Example 3 is repeated using $^{125}I^-$.

Example 10

The method of Example 4 is repeated using $^{125}I^-$.

Example 11

The method of Example 5 is repeated using $^{125}I^-$.

Example 12

7-Iodo-8-quinolinol is prepared from 5-amino-8-quinolinol via a Gattermann reaction according to the method of Gershon et al (J. Heterocycl. Chem., 1971, 8(1), 129-131) by treatment of the amine with sodium nitrite to permit covalent attachment of ^{125}I in the presence of copper and $H^{125}I$ which is formed from $Na^{125}I$ at the pH of the reaction. The reaction product is extracted into a small volume of methylene chloride. A piece of carbon yarn 0.076 mm in diameter and 5 mm long (from Alpha Aesar) is heated in a tube furnace above 400 °C in an argon flow, cooled in the absence of moisture and added to the methylene chloride solution. The solvent is allowed to evaporate to leave the reaction product adsorbed on the carbon yarn. The yarn is placed in a titanium can and the can is sealed to form a seed suitable for use in brachytherapy.

Example 13

Anthranilic acid is diazotized and treated with $K^{125}I$ according to the method of Friedman L. and Logullo F.M. (Angew. Chem., 1965, 77, 217) to provide a mixture of products comprising radioactive iodinated aromatic organic

compounds. This mixture is adsorbed onto carbon yarn according to the method of Example 12.

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